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Depression in Childhood and Adolescence

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Abstract

Objective: To review recent evidence on child and adolescent depression. **Method:** Narrative review. **Results:** Rates of unipolar depression are low before puberty, but rise from the early teens, especially among girls. Concurrent comorbidity with both disruptive and emotional disorders is common, especially among younger children; across age, youth depression may be preceded by both anxiety and disruptive behaviour disorders, and increase risk for alcohol problems. Adolescent depression is associated with a range of adverse later outcomes including suicidality, problems in social functioning and poor physical and mental health. Across development, a family history of depression and exposure to stressful life events are the most robust risk factors for depression. Familial transmission involves both psychosocial and heritable processes; genetic and environmental influences also combine to influence risk. Neurocognitive and neuroendocrine pathways have been established, but contributors to the adolescent rise in risk, and the female preponderance later in development, remain to be clarified. Depressed youth benefit from psychological therapy or antidepressant medication or their combination; however, treatment effects are moderate. **Conclusions:** Despite considerable progress in understanding developmental trajectories to depression, more needs to be done to identify disease mechanisms that may serve as intervention targets early in the life course.

Key words: *aetiology, epidemiology, anti-depressant, depression, adolescence*

Résumé

Objectif: Examiner les données probantes récentes sur la dépression chez les enfants et les adolescents. **Méthode:** Revue narrative. **Résultats:** Les taux de dépression unipolaire sont faibles avant la puberté, mais s'accroissent à compter du début de l'adolescence, surtout chez les filles. La comorbidité concurrente avec des troubles perturbateurs et émotionnels est fréquente, en particulier chez les jeunes enfants; pour tous les groupes d'âge, la dépression chez les jeunes peut être précédée d'anxiété et de troubles de comportement perturbateur, et d'un risque accru de problèmes d'alcool. La dépression adolescente est associée à une série de résultats ultérieurs indésirables, notamment la suicidabilité, des problèmes de fonctionnement social et une mauvaise santé physique et mentale. Durant le développement, des antécédents familiaux de dépression et d'exposition à des événements stressants de la vie constituent les facteurs de risque les plus marqués pour la dépression. La transmission familiale fait appel à des processus tant psychosociaux qu'héréditaires; les influences génétiques et environnementales se combinent également pour influencer le risque. Les trajectoires neurocognitives et neuroendocriniennes ont été établies, mais les contributeurs à la hausse du risque chez les adolescents, et la prépondérance féminine ultérieure dans le développement ne sont pas encore bien définis. Les adolescents déprimés bénéficient de la thérapie psychologique ou des antidépresseurs ou d'une combinaison des deux; cependant, les effets du traitement sont modérés. **Conclusions:** Malgré que notre compréhension des trajectoires développementales de la dépression ait fait des progrès considérables, il faut faire davantage pour identifier les mécanismes de la maladie qui peuvent servir de cibles aux interventions en début de cours de la maladie.

Mots clés: *étiologie, épidémiologie, antidépresseur, dépression, adolescence*

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Less than three decades ago depression was seen as a predominantly adult disorder: children were considered too developmentally immature to experience depressive disorders, and adolescent low mood was seen as part of 'normal' teenage mood swings. Developmental studies have been central in modifying that view. Few would now doubt the reality of child and adolescent depressive disorders, or that youth depression is associated with a range of adverse outcomes including social and educational impairments as well as both physical and mental health problems later in life (see Thapar, Collishaw, Pine, & Thapar, 2012). In addition, however, while research on the course and correlates of depression has identified important similarities across development, it has also highlighted age-related variations; as a result, investigators continue to evaluate the extent to which childhood, adolescent and adult onset depressions reflect the same underlying condition (Kaufman, Martin, King, & Charney, 2001). This review provides a brief introduction to recent evidence in these areas, focusing in particular on:

- i) descriptive aspects of depressive disorders in childhood and adolescence;
- ii) current understandings of risk processes and mechanisms; and,
- iii) evidence-based treatments for depressive disorders in youth.

Clinical features and epidemiology

Diagnostic criteria for unipolar depression centre on core symptoms of persistent and pervasive sadness, along with a loss of interest or pleasure in activities; associated symptoms include low self-esteem, excessive guilt, suicidal thoughts or behaviours, sleep and appetite disturbances, and psychomotor agitation or retardation. In the main, these criteria are applied independent of age (including, with age-appropriate modifications, in recent studies of pre-schoolers; Luby, 2010). In the DSM-IV criterion set, however, marked irritability is allowed as the cardinal mood symptom for children and young people only.

Past-year estimates of the prevalence of major depressive disorders in early adulthood range from 10%-17% (Moffitt et al., 2010), with women about twice as likely to be affected as men. Earlier in development rates are much lower, and show a distinct age- and gender-related profile. Depression is relatively uncommon in pre-pubertal children (1-2%), and rates differ little between boys and girls (Egger & Angold, 2006). Levels then begin to rise in the early teens, more sharply in girls than in boys. As a result, by the mid-teens the median 12-month prevalence of unipolar depression is in the region of 4-5%, and the female preponderance characteristic of adult depression is clearly established (see Thapar et al., 2012).

Throughout the life course depression is comorbid with other psychiatric disorders. In adulthood, the most prominent associations are with anxiety. In school-aged samples (see e.g. Ford, Goodman, & Meltzer, 2003) around two-thirds of young people with depression show at least one comorbid disorder, and over 10% show two or more; overlaps with disruptive disorders (Attention Deficit Hyperactivity Disorder [ADHD], Oppositional Defiant Disorder [ODD], and Conduct Disorder [CD]) are as common as with other emotional diagnoses at this stage. In pre-school samples rates of comorbidity are even higher, with three in every four depressed preschoolers reported as showing other vulnerabilities (Egger & Angold, 2006; Wichstrom, Berg-Nielsen, Angold, Egger, Solheim, & Sveen, 2012). When multiple disorders co-occur in this way, some two-way associations may primarily reflect overlaps among associated disorders. ADHD-depression comorbidity seems primarily of this kind, mediated by the strong links of both disorders with ODD/CD. ODD also appears to play a key role in pre-school samples; it is the most common concomitant of depression in very young children, and mediates links with both ADHD and anxiety at this stage. As Egger and Angold (2006) note, these findings raise queries over the extent to which depressive disorders in preschoolers are indeed equivalent to those seen later in development, or whether instead they may index a more global syndrome of emotional and behavioural dysregulation.

Continuities and discontinuities across development

Clinical studies of youth depression confirm that it is a chronic and recurrent condition: although most episodes remit within a year, the risk of recurrence in clinical samples is high, with 50-70% likely to develop a further episode within five years (see e.g. Dunn & Goodyer, 2006). Follow-ups of epidemiological samples - where many cases will be less severe - also highlight poor outcomes, with implications for young people's social functioning as well as for their later mental health. In addition to their public health significance, findings of this kind can be informative in aetiological terms. Evidence of *homotypic continuities* (the persistence of the same disorder over time), for example, is suggestive of a single disease process manifesting itself robustly at different stages of development. *Heterotypic continuities*, by contrast, may suggest either that the same underlying disease process manifests differently across development, or that one disorder (or its associated impairments) functions as a risk factor for another. Evidence for both of these processes has been found for child and adolescent depression.

Beginning with homotypic continuities, follow-ups of pre-school samples provide evidence of continued risk for depression at least into the early school years (Luby, 2010). Later in development the picture is more complex. First, while most follow-ups of adolescent depression find

increased risks of depression and suicidality in adulthood, these links are strongly attenuated in multivariate analyses that take account of the effects of comorbid disorders such as ODD (see e.g. Copeland, Shanahan, Costello, & Angold, 2009). Second, though few studies have yet examined adult outcomes of childhood depression, those that have done so (see e.g. Harrington, Fudge, Rutter, Pickles, & Hill, 1990; Copeland et al., 2009) have found little or no increased risk of depression in adult life. If replicated, these findings provide further pointers to the possibility that childhood depression differs in important ways from its later onset counterparts.

Turning to heterotypic continuities, links with three other disorder groupings (anxiety disorders, alcohol and substance use and CD/ODD) have attracted particular interest. Associations between depression and anxiety are high throughout the life course, but their order of emergence appears to vary systematically across development. Between childhood and early adolescence anxiety typically precedes depression (Wittchen, Kessler, Pfister, & Lieb, 2000). From later adolescence onwards, however, the temporal sequence runs in both directions: anxiety predicts depression, but depressive disorders also predict later anxiety (Moffitt et al., 2007). While these associations seem likely to reflect varying expressions of the same underlying liability, other heterotypic continuities may be better conceptualized as psychopathological progressions, whereby one disorder contributes, directly or indirectly, to risk for another. In relation to alcohol use, for example, though findings are complex, commentators are now arguing for a distinct internalizing pathway to alcohol use disorders, with self-medication a central intervening mechanism (Hussong, Jones, Stein, Baucom, & Boeding, 2011). Finally, a variety of processes may underlie the strong risk for depressive disorders associated with prior antisocial behaviour and conduct problems. In part, associations of this kind may reflect environmentally-mediated effects of selection into stress-prone environments. In addition, recent evidence points to a specific increased risk for depression associated with an irritable sub-component of ODD that shares genetic associations with depression (Stringaris, Zavos, Leibenluft, Maughan, & Eley, 2012).

Risk processes and mechanisms

Depression is a complex disorder, and a variety of risk factors and causal pathways are likely to be involved. Evidence for both inherited and psychosocial risks has been established for many years; more proximal neurocognitive and neuroendocrine mechanisms are now also beginning to be better understood. A full consideration of the aetiology of depression is beyond the scope of this paper; instead, we highlight ways in which a developmental perspective can help clarify understanding of causal mechanisms.

Across development, studies of adults, adolescents, children and pre-schoolers all point to a family history of depression and exposure to stressful life events as the most robust risk factors for depression. Depression runs in families, with three-to-four fold elevated rates in the offspring of depressed parents. Inherited factors partly account for these effects, although genome wide association studies have yet to identify replicated gene variants associated with depression (Thapar et al., 2012). In addition, genetically informative studies suggest that psychosocial mechanisms are also implicated in familial transmission, with adoption studies, for example, showing an excess risk of depression in the offspring of depressed mothers even in biologically unrelated mother-child pairs (Tully, Iacono, & McGue, 2008).

Psychosocial risks include family bereavement, separations and conflict, child maltreatment and neglect, and peer conflict and bullying (see e.g. Jaffee et al., 2002; Kendler, Thornton, & Gardner, 2000). Chronic stressors affecting relationships appear to have a greater impact than isolated acute events, especially in females (Thapar et al., 2012). In addition, there are pointers to aetiological differences between child-, adolescent-, and adult-onset depression. First, the balance of inherited and environmental risks appears to vary across development, with twin studies consistently reporting *lower* heritability estimates for depression in childhood than in adolescence (Thapar & Rice, 2006). Second, it has been suggested that juvenile- and adult-onset depression show different psychosocial risk profiles, with juvenile onset more strongly associated with childhood family adversity, parental neglect, and problematic peer relationships (Jaffee et al., 2002; Hill, Pickles, Rollinson, Davies, & Byatt, 2004). These studies did not distinguish pre- and post-pubertal onset within the 'juvenile' onset group. One that has, however, suggests that such findings reflect recency of risk exposure, and that concurrently-assessed stressors are on the whole equally strongly associated with child-, adolescent- and adult-onset depression (Shanahan, Copeland, Costello, & Angold, 2011). In addition, individual level data suggest a diminishing role of stressful events in triggering the onset of successive depressive episodes (Kendler et al., 2000). Finally, childhood adversities including poverty, sexual abuse and psychopathology may also present distal risks for depression later in the life course (Hill et al., 2004; Shanahan et al., 2011) via selection into more disadvantaged and stressful life circumstances.

Research on gene-environment interplay suggests that genes and environments combine to influence vulnerability, with heritable factors increasing risk of both *exposure* to stressful environments (gene-environment correlation, Lau & Eley, 2008), and *susceptibility* to psychosocial stress (gene-environment interaction, Caspi et al., 2003; Uher & McGuffin, 2010). The serotonin transporter gene variant 5-HTTLPR has received the greatest attention here, with evidence that one variant of the gene increases risk for depression in those exposed to stressful life events or

childhood maltreatment (Caspi et al., 2003). Animal and experimental neuroscience evidence supports the biological plausibility of gene-environment interactions such as this (Rutter, Thapar, & Pickles, 2009). Not all findings are consistent, however; in part, this may reflect variations in gene-environment interactions by age and/or gender, with, for example, more robust evidence in post-pubertal females (Uher & McGuffin, 2010). There is also evidence from animal models and post mortem brain tissue of depressed humans (Schroeder, Krebs, Bleich, & Frieling, 2010) that epigenetic alterations in gene expression are implicated in depression; developmental studies are required to track such epigenetic influences across the life span.

Specific neurocognitive and neuroendocrine pathways involved in the development of depression have also begun to be identified. As outlined in a recent review (Thapar et al., 2012), these pathways are regulated by activity in neural circuits involved in the processing of threats and rewards. In both instances the circuits involved have been linked to risk for depression in evidence from animal research, human imaging and pharmacological studies. The first circuit - involved in processing of threat - connects the amygdala, hippocampus and prefrontal cortical regions and is associated with HPA axis activity. The second, 'reward', circuit connects the striatum, prefrontal cortex and ventral dopamine-based systems. Both circuits continue to mature and show emergent sex differences in adolescence (Forbes & Dahl, 2005; Thapar et al., 2012).

From a developmental perspective a key issue concerns factors that contribute to the post-pubertal rise and emergent sex difference in depression in adolescence. A variety of mechanisms has been proposed here, including gender differences in cognitive processing of stressful events and coping styles: greater exposure or sensitivity to psychosocial stress in adolescent girls; hormonal changes associated with pubertal maturation; and, changes in underlying brain development (Angold, Costello, Erkanli, & Worthman, 1999; Hyde, Mezulis, & Abramson, 2008). Disentangling particular causal mechanisms is difficult given the extent of cognitive, psychosocial and biological change occurring in adolescence, and the likelihood of complex interactions between different factors and mechanisms. More evidence is also needed on how far the aetiological mechanisms discussed here are specific to depression or instead contribute to broad risk for psychopathology, and may thus help account for comorbidity.

Treatment and prevention of depression in youth

Most treatments for youth depression were first developed in the treatment of adults, and subsequently used with young people. In contrast to the developmental focus of much epidemiologic and neurobiologic research in depression, treatment studies have so far rarely directly investigated

whether developmental factors have predictive or moderating effects on treatment outcomes. In part this may reflect the practical difficulties of conducting therapeutic studies with large enough sample sizes to allow robust comparisons across developmental periods.

Treatments for preschoolers with depression are currently being evaluated (Luby, 2010). We focus here on the three main evidence-based treatments for depression in older children and adolescents: pharmacotherapy with fluoxetine or another serotonin reuptake inhibitor (SRI); cognitive and behavioural therapy (CBT); and, interpersonal therapy (IPT). Most current evidence concerns the short-term effects of these treatments as measured in Randomized Control Trials (RCTs); there is little information at this stage about their influence on longer-term outcomes.

Tricyclic antidepressants, while useful in adults, are not effective for the treatment of depression in prepubertal children, and of dubious effect in adolescents (Hazell, O'Connell, Heathcote, & Henry, 2002); the reasons for these developmental differences remain poorly understood. By contrast, fluoxetine has meta-analytic evidence from RCTs for the treatment of depression in both children and adolescents (age range 6-18 years, Hetrick, Merry, McKenzie, Sindahl, & Proctor, 2007). Other SRIs have not been shown to be consistently effective, although escitalopram was recently approved for the treatment of adolescent depression in the United States on the basis of an RCT (Emslie, Ventura, Korotzer, & Tourkodimitris, 2009).

When using SRIs, clinicians should be aware of a series of issues. First, the effects of SRIs on youth depression are at best moderate, in part because of the high placebo response rates in young people (Bridge, Birmaher, Iyengar, Barbe, & Brent, 2009). Second, evidence on the effectiveness of SRIs is still limited and not without methodological problems, such as high rates of attrition. Third, while SRIs may be useful for relieving the symptoms of depression, their effects on other outcomes, including indicators of quality of life, are less compelling. Finally, there is an ongoing controversy about how SRIs are related to suicidality in youth, with evidence (Hetrick et al., 2007) to suggest that suicidal ideation is higher in those treated with fluoxetine compared to those treated with placebo in RCTs. However, it is clear that the risk of suicidal ideation is far outweighed by the benefit conferred by treatment with anti-depressants: the number needed to treat for anti-depressants is ten, while the number needed to harm with anti-depressants is 143. This suggests that there are good reasons to prescribe anti-depressants in young people while also closely monitoring for suicidality along with other side effects (e.g. emergence of manic symptoms or agitation).

CBT is also widely recommended for the treatment of depression in children and adolescents. In some countries, such as the United Kingdom, it is considered the first line treatment for mild depression and an adjunct for moderate

to severe depression. However, the meta-analytic evidence suggests effects that are in the lower moderate range (less than 0.3; Weisz, McCarty, & Valeri, 2006). In the US Treatment of Adolescents with Depression Study (TADS), adolescents receiving CBT did not do better than those on placebo (March et al., 2004).

Evidence on the effects of combining medication with CBT is mixed. In the TADS, combined CBT with fluoxetine led to significantly greater improvement than fluoxetine alone. Conversely, in the UK Adolescent Depression, Antidepressants and Psychotherapy Trial (ADAPT), there was no additional benefit from adding CBT to fluoxetine (Goodyer et al., 2007). Perhaps the most compelling evidence comes from the Treatment of Resistant Depression in Adolescents (TORDIA) study, where switching from fluoxetine to another SRI achieved significantly better response in those who also received CBT (Brent et al., 2008).

Finally, several trials suggest that interpersonal therapy (IPT) is a useful treatment for depression, with evidence of effectiveness in schools (Mufson et al., 2004) and international settings (Bolton et al., 2007). At this stage, however, the dissemination of IPT remains limited.

Other factors affecting treatment planning will include the presence of comorbid disorders and maternal mental health. Surprisingly, there is little trial evidence on how to treat comorbidity in depression - is it better to treat the depression or the comorbid condition or both, and under which circumstances? Clinicians usually make case-by-case decisions, treating first the condition that is either more chronic or appears to be the most severe. In relation to maternal mental health, evidence suggests that treatment of maternal depression can help alleviate depression in offspring. Results from a trial of mothers with depression treated with medication showed that remission of maternal depression was associated with a significant improvement in children's depression, whereas persistence of maternal illness was associated with new onset of children's depression (Weissman et al., 2006). Finally, clinicians should look out for new technologies that might enable them to deliver effective treatments with relatively little resources. Recent evidence suggests, for example, that with adolescents computerized CBT may be at least as effective as treatment as usual, including face-to-face counseling with clinical psychologists (Merry et al., 2012).

Preventing depression using psychological (mainly cognitive and behavioural) techniques seems feasible (Merry et al., 2011), although it is likely to be most effective in children and adolescents at high risk by virtue of subthreshold symptoms, a prior diagnosis of depression, or family history. One of the methodologically most rigorous studies in this area compared a group-based cognitive and behavioural prevention programme to usual care alone in adolescents at high risk as a result of prior depression or current subthreshold symptoms (Garber et al., 2009). The rate of

incident depression and of self reported depressive symptoms was significantly lower in those randomised to the prevention arm.

Conclusions

As this brief overview suggests, developmental studies have made key contributions to our understanding of child and adolescent depression, and the complex interactions between inherited, psychological and social factors that influence short- and long-term risk. A developmental perspective has been crucial in understanding how distal and proximal risks interact with normal developmental processes to affect vulnerability for depression in childhood, adolescence and adulthood, and in highlighting both similarities and differences between depressive phenomena arising at these different stages.

Acknowledgments / Conflicts of Interest

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